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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOESEN, AGNIESZKA	

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1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/558,276	WISNIEWSKI ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *5-8,11-19,24-27,29-37,40-44 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,10,20-23,28,38,39,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/06 and 11/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received November 8, 2007.

Election/Restrictions

Applicant's election without traverse of group I, claims 1-10, 20-28, 38, 39 and 41-50 and the species of SEQ ID NO: 4 is acknowledged. Applicants contend that claims 1-4, 9, 10, 20-23, 28, 38, 39, and 45-50 read on the elected species. The Office agrees that claims 1-4, 9, 10, 20-23, 28, 38, 39, 45 and 46 read on the elected species of SEQ ID NO: 4, however claims 47-50 do not read on elected species because the claims recite the non-elected SEQ ID NO: 1 without reciting the elected SEQ ID NO: 4. Thus claims 5-8, 11-19, 24-27, 29-37, 40-44, and 47-50 are withdrawn because the claims are drawn to the non-elected invention.

Claims 1-4, 9, 10, 20-23, 28, 38, 39, 45 and 46 are under consideration in the present Office action.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on October 16, 2006 and November 18, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner. It is noted that the German reference by Gerstmann et al., Z Neurol., 1936, Vol. 154, p. 736-762 submitted in the IDS of November 18, 2005 has not been considered because the English translation has not been provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9, 10, 20-23, 28, 38, 39, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the immunogenic composition comprising the mammalian prion protein and the immunogenic composition comprising an attenuated *Salmonella typhi* bacterium transfected with mammalian prion protein, does not reasonably provide enablement for the intended use of the compositions as a pharmaceutical or vaccine.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un)predictability of the art, and the breadth of the claims.

Claims are drawn to a vaccine and a pharmaceutical composition comprising a mammalian prion protein and an adjuvant eliciting a humoral immune response. Claims are drawn to a vaccine composition comprising an attenuated *Salmonella typhi* bacterium transfected spp strain transformed with a vector capable of expressing a mammalian prion protein. The claims are rejected because the specification does not provide sufficient enablement for the full scope of the claimed invention. Particularly the disclosure does not enable the skilled artisan for the intended use of the claimed compositions as vaccines or pharmaceuticals.

The term "vaccine" implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease. A pharmaceutical composition can be interpreted to be a drug; a drug by definition is an agent intentioned for the use in the diagnostics, mitigation, treatment, cure, or prevention of disease in humans or in animals.

The present specification contemplates using claimed vaccine compositions for induction of humoral immune responses against the prion protein, and for eliciting mucosal immune responses that would prevent, delay, or reduce the formation of the aggregates, deposits, or fibrils involving the peptides associated with prionoses. The specification discusses that animal

studies could be designed to "evaluate preventive or prophylactic vaccination (i.e., vaccine administration before any symptom of disease) or treatment of an already existing condition (i.e., vaccine administration after a disease symptom)" (see [0014] and [0068-0071]).

The specification provides working examples showing generation of mucosal immune responses in mice immunized with *Salmonella typhimurium* comprising cDNA encoding prion protein (Example 2). Example 4 shows that 60% of mice immunized with the *Salmonella typhimurium* comprising cDNA encoding prion protein survived infection with prion protein containing brain homogenates, while between 80 and 90% of control mice died due to infection. It is acknowledged that immunization of mice with the composition of the present invention has contributed to the survival of challenged mice as compared to the control mice. However, based on the working examples presented in the specification, the skilled artisan would be unable to reasonably conclude that immunization with the *Salmonella typhimurium* comprising cDNA encoding prion protein can induce protective immune responses in humans. It is noted that claims broadly encompass all mammalian prion proteins and therefore include human prion proteins and the intended use of the claimed vaccines to prevent prion infection in humans. The skilled artisan would be required to conduct an undue amount of experimentation in order to reasonably conclude that the compositions of the present invention could be successfully used to prevent prion infection in humans and in animals other than mice.

The specification does not set forth sufficient teachings to allow one skilled in the art to use the claimed vaccines or pharmaceutical preparations to treat or prevent prion disease. The specification does not provide teachings to establish effective dosages or methods of administration of a vaccine comprising a mammalian prion protein or a vaccine comprising an

attenuated *Salmonella typhi* bacterium transformed with a vector expressing a mammalian prion protein to treat or prevent prion disease. The specification provides no description and exemplification of how to use the pharmaceutical composition, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure of a disease in the subject to which the substance is administered. The working examples provided do not give sufficient guidance to allow one skilled in the art to practice the full scope of the invention with a reasonable expectation of success.

Bachman et al. (Patent Application Publication No.: 2003/0219459 A1) teaches that there has been little evidence that vaccines might be effective for protection against prion diseases, in particular, since it is usually difficult to induce antibody responses to self-molecules by conventional vaccination (see [0011]). Thus prion proteins are regarded as poor immunogens. Vaccination with recombinant mouse prion protein delays the onset of disease but does not prevent the disease (Sigurdsson et al. Immunization delays onset of prion disease in mice. American Journal of Pathology, 2002, Vol. 161, No. 1, pp. 13-17). Also successful observations made in mice cannot be readily translated to treatment in humans as evidenced based on the problems reported with the Aβ1-42 vaccine for Alzheimer's disease (Sigurdason et al., 2002, see page 16, column 1). Irani et al. (Annual Reviews in Medicine, 2003, Vol. 54, p. 305-319.) and Coulthart et al. (Canadian Medical Association, 2001, Vol. 165, p.51-58) reviews the research efforts in the field of diagnosis and prevention of prion diseases. Currently, there is no treatment or preventive means for prion disease. Because of a very long time period (more than 10 years in humans) which elapses between infection and the appearance of the first clinical symptoms, and because the diagnosis can be only performed postmortem, it would have been nearly

impossible to evaluate the efficacy of the prevention of the prion diseases in humans (Georgieva, Experimental Pathology and Parasitology, 2002, p. 60-63).

Thus, the nature of the invention and the state of prior art have not provided reasonable expectation of success in the treatment of prion diseases. For the above discussed reasons, it appears that undue experimentation would be required to practice the claimed invention with a reasonable expectation of success. While it is within the level of one skilled in the art to make a composition comprising a mammalian prion protein and a composition comprising an attenuated *Salmonella typhi* bacterium transformed with a vector capable of expressing a mammalian prion protein, it is beyond the skilled artisan to successfully use the claimed compositions for treatment and/or prevention of prion disease.

In conclusion, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately determine whether the compositions of the instant application do in fact have a therapeutic and preventive effect against prion disease.

Thus, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the therapy and prevention of prion diseases, that one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately extrapolate whether said composition would actually have a therapeutic and preventive effect against prion disease.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the *Salmonella* spp strains, *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 are required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 strains. See 37 CFR 1.802.

One cannot practice the claimed invention without access to the *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 strains because the said strains are necessary in order to generate the bacterial vector comprised in the claimed composition. Therefore, access to *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 strains is required to practice the invention. The specification does not provide a repeatable method for isolating the *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 strains and these strains do not appear to be readily available material. Neither the specification nor the prior art provide sufficient teachings with regard to whether the claimed bacterial strains are publicly available. Deposit of *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 in a

recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph, because the bacterial strains would be readily available to the public to practice the claimed invention, see 37 CFR 1.801- 37 CFR 1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 9, 38, and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1).

Claims are drawn to a vaccine and a pharmaceutical composition comprising a mammalian prion protein and an adjuvant eliciting a humoral immune response. The prion protein comprises an amino acid sequence which is a member of the group consisting of residues 93-156 or residues 123-225 of SEQ ID NO: 4. The adjuvant is aluminium hydroxide. The composition comprises alum as a pharmaceutically acceptable excipient.

It is noted the claims recite an open language with regard to the sequences represented by residues 93-156 and 123-225 of the SEQ ID NO: 4. Therefore the claims are anticipated by a full length SEQ ID NO: 4 comprising residues 93-156 and 123-225. It is also noted that elected SEQ ID NO: 4 represents elk prion protein (see specification page 4).

Bachman et al. disclose a composition comprising a mammalian prion protein, wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4 and represents the elk prion protein (see SEQ ID NO: 82 of the sequence listing, and claims 1, 14, and 15). While the intended use of the present composition is not limiting, it is noted that Bachman et al. disclose a vaccine and a pharmaceutical composition comprising prion proteins (see claims 44-57, [0003], [0021], [0027], [0079]). Bachman et al. disclose pharmaceutical and vaccine compositions comprising mammalian prion proteins formulated with an adjuvant aluminium hydroxide eliciting humoral immune response and alum as a pharmaceutically acceptable excipient (see [0035], [0080], and Example 15).

Thus by this disclosure Bachman et al. anticipate the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) as applied to claims 1-3 and further in view of Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285, in IDS of 11/18/2005).

Claim is drawn to the composition comprising a mammalian prion protein wherein all amino acids of the prion protein are D-amino acids.

Bachman et al. teach a composition comprising a mammalian prion protein, wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4 and represents the elk prion protein (see SEQ ID NO: 82 of the sequence listing, and claims 1, 14, and 15), as discussed above. Bachman et al. does not teach the prion protein wherein all amino acids are D-amino acids.

Benkirane et al. teach that changing the amino acids within an antigenic peptide from an L-residue to the corresponding D-residue drastically increases the antigenicity of the peptide and contributes to the generation of high levels of IgG3 antibodies in immunized animals (see the entire document, particularly page 26279 and Discussion).

Thus based on the teaching of Benkirane et al., it would have been *prima facie* obvious to the person skilled in the art to provide a pharmaceutical composition designed for induction of immune responses, wherein the amino acids within the antigenic protein are D-amino acids.

One would have been motivated to provide Bachman's pharmaceutical composition comprising mammalian prion protein wherein the amino acids of the prion protein are D-amino acids, because Benkrine et al. teach that changing the amino acids within an antigenic peptide from L- to D- amino acids results in increased antigenicity and thus better immunogenicity of the peptide.

One would have had a reasonable expectation of success to provide a composition comprising a mammalian prion protein wherein all amino acids are D-amino acids, because the means required for the synthesis of proteins containing D-amino acid residues have been available to the skilled artisan at the time of the present invention as evidenced by Benkriane et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Application Publication No.: 2003/0219459 A1) as applied to claim 1 and further in view of Clemens et al. (US Patent 6,440,423 B1) and Kleanthous et al. (US Patent 6,585,975 B1).

Claims are drawn to the composition comprising a mammalian prion protein wherein the prion protein is covalently attached to the cholera toxin subunit B.

Bachman et al. teach a composition comprising a mammalian prion protein, as discussed above. Bachman et al. does not teach the composition wherein the prion protein is covalently attached to the cholera toxin subunit B.

Clemens et al. teach cholera toxin subunit B as an effective adjuvant comprised in vaccine compositions comprising viral or bacterial antigens (see the entire document, particularly claims 1-7 and column 4, lines 28-51). It is noted that Clemens et al. also teach another adjuvant species recited in claim 9, the heat-liable enterotoxin (LT) (see column 9, lines 60-67 and column 10, lines 1-67). Clemens et al. do not expressly teach covalent attachment of cholera toxin subunit B to the antigenic protein. Kleanthous et al. teach covalent attachment of cholera toxin subunit B adjuvant to the antigenic protein (column 5, lines 1-20).

It would have been *prima facie* obvious to covalently attach cholera toxin subunit B to the prion protein. One would have been motivated to covalently attach Clemens' cholera toxin subunit B to Bachman's prion protein, because Clemens' teach that cholera toxin subunit B

adjuvant allows for improved mode of oral immunization and development of serum and mucosal antibodies against pathogenic microorganisms and that the cholera toxin subunit B is useful in combination with any specific antigen where a specific neutralizing antibody response would be beneficial in ablating the disease state associated with the antigen (see column 9, lines 5-26).

One would have had a reasonable expectation of success to provide a pharmaceutical composition comprising prion protein covalently attached to the cholera toxin subunit B, because a covalent attachment of cholera toxin subunit B to antigens of interest has been successfully practiced in the art as evidenced by Kleanthous et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 20-22, 28 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) in view of Lu et al. (US Patent 5,733,760) and Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005).

Claims are drawn to a vaccine composition comprising an attenuated *Salmonella typhi* bacterium transfected spp strain transformed with a vector capable of expressing a mammalian prion protein, wherein the prion protein comprises an amino acid sequence which is a member of the group consisting of residues 93-156 or residues 123-225 of SEQ ID NO: 4. The Salmonella strain is *Salmonella typhimurium* LVR01.

It is noted the claims recite an open language with regard to the sequences represented by residues 93-156 and 123-225 of the SEQ ID NO: 4. Therefore the claims are anticipated by a full length SEQ ID NO: 4 comprising residues 93-156 and 123-225. It is also noted that elected SEQ ID NO: 4 represents elk prion protein (see specification page 4).

Bachman et al. teach a composition comprising a mammalian prion protein, wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4 and represents the elk prion protein (see SEQ ID NO: 82 of the sequence listing, and claims 1, 14, and 15). Bachman's prion protein is comprised within the viral like particle and not the attenuated *Salmonella typhi* bacterium transfected spp strain as required by the present claims.

Lu et al. teach vaccine compositions comprising attenuated *Salmonella* vectors expressing heterologous DNA encoding viral antigens from HIV and HCV viruses (see the entire document, particularly claims 1-9, column 5, lines 65-67, column 10, lines 19-60). While Lu et al. teach *Salmonella typhi, Salmonella typhimurium, and Salmonella enteritidis*, (see column 6, lines 65-67, Lu et al. does not teach the specific *Salmonella* strains as recited in the present claim 28.

Chabalgoity et al. teach *Salmonella typhimurium* LVR01 strain expressing heterologous antigens encoding binding fatty acid protein from *Echinococcus granulosus* (see the entire document, particularly Materials and Methods).

It would have been *prima facie* obvious to express mammalian prion protein in *Salmonella* bacterial vectors used for expression of heterologous antigens. Therefore it would have been obvious to provide a composition comprising attenuated *Salmonella typhi* bacterium

transfected spp strain transformed with a vector capable of expressing a mammalian prion protein.

One would have been motivated to substitute Lu's attenuated *Salmonella* vectors for Bachman's viral particles and express mammalian prion proteins in *Salmonella* vectors because Lu et al. teach that their *Salmonella* vectors are particularly effective for induction of mucosal protective immune responses against mucosally transmitted infectious agents. Lu et al. also teach that attenuated Salmonella vectors are effective vectors for delivery of desired antigens because the bacteria grow rapidly and do not require growth in cell culture, thus allowing large scale production of vectors (see column 1, lines 19-55).

One would have been motivated to use Chabalgoity's *Salmonella typhimurium* LVR01 strain for expression of Bachman's prion proteins because Chabalgoity et al. teach that heterologous antigens expressed in LVR01 effectively elicits humoral and cellular immune responses in animals (see the entire document, particularly Results and Discussion on page 468).

One would have had a reasonable expectation of success to provide a composition comprising an attenuated *Salmonella typhi* bacterium and particularly *Salmonella typhimurium* LVR01 transformed with a vector capable of expressing a mammalian prion protein because the technology used for generation of bacterial recombinant vectors has been available to the skilled artisan at the time of the present invention. Moreover, the bacterial recombinant vectors expressing heterologous antigens have been successfully made in the art at the time of the invention as evidenced by Lu et al. and Chabalgoity et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachmann et al. (Patent Application Publication No.: 2003/0219459 A1) in view of Lu et al. (US Patent 5,733,760) as applied to claims 22 and 45 and further in view of Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285).

Claims are drawn to a vaccine composition comprising an attenuated *Salmonella typhii* bacterium transfected spp strain transformed with a vector capable of expressing a mammalian prion protein, wherein all amino acids of the prion protein are D-amino acids.

Bachman et al. and Lu et al. teach a vaccine composition comprising an attenuated *Salmonella typhii* bacterium transfected spp strain transformed with a vector capable of expressing a mammalian prion protein as discussed above.

Benkirane et al. teach that changing the amino acids within an antigenic peptide from an L-residue to the corresponding D-residue drastically increases the antigenicity of the peptide and contributes to the generation of high levels of IgG3 antibodies in immunized animals (see the entire document, particularly page 26279 and Discussion).

Thus based on the teaching of Benkirane et al., it would have been *prima facie* obvious to the person skilled in the art to provide a pharmaceutical composition designed for induction of immune responses, wherein the amino acids within the antigenic protein are D-amino acids.

One would have been motivated to provide Bachman's and Lu's pharmaceutical composition comprising attenuated *Salmonella typhii* transformed with a vector capable of expressing a mammalian prion protein wherein the amino acids of the prion protein are D-amino acids, because Benkirane et al. teach that changing the amino acids within an antigenic peptide from L- to D- amino acids results in increased antigenicity of the peptide.

One would have had a reasonable expectation of success to provide a composition comprising a mammalian prion protein wherein all amino acids are D-amino acids and to successfully use this composition for immunization purposes, because the means required for the synthesis of proteins containing D-amino acid residues have been available to the skilled artisan at the time of the present invention as evidenced by Benkirane et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AB

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